HETEROCYCLES, Vol. 53, No. 5, 2000, pp. 1085 - 1110, Received, 7th February, 2000

TOTAL SYNTHESIS OF OPTICALLY ACTIVE *m*-PHENYLENE PGI_2 DERIVATIVE: BERAPROST

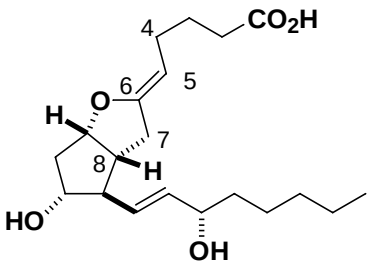
Hisanori Wakita,[a] Hideo Yoshiwara,[a] Hisao Nishiyama,[b] and Hiroshi Nagase*[a]

[a]Basic Research Laboratories, Toray Industries, Inc., 1111 Tebiro, Kamakura, Kanagawa, 248-8555 Japan

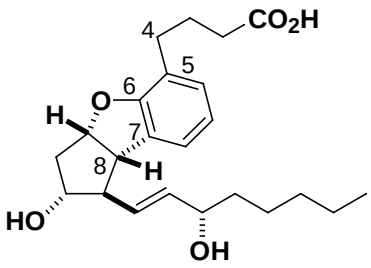
[b]School of Material Science, Toyohashi University of Technology, Tempakucho, Toyohashi, Aichi, 441-8580 Japan

Abstract-The optical isomers of *m*-phenylene PGI_2 derivative, Beraprost, were synthesized in practical scales from optically active carboxy-cyclopenta[*b*]benzofurans (**12** and **13**) by Wittig and Wadsworth reactions as key reactions *via* the intermediate diols (**16a** and **16b**).

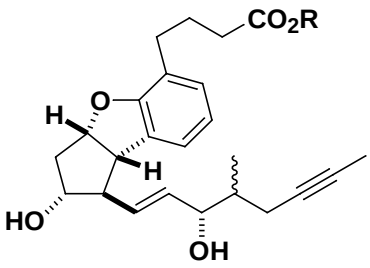
PGI_2, one of natural prostaglandins, has been focused on since its discovery due to biological activities such as inhibition of platelet aggregation or vascular vasodilation.[1] However, it readily decomposes in acidic or even neutral media because of instability of its enol ether linkage at C5-C6-O. We have been developed a new PGI_2 analogue (**1**) with *m*-phenylene skeleton at C5-C6-C7 in order to stabilize the enol ether part in natural PGI_2 (Figure 1).[2-6] We have also developed the stable analogue named Beraprost, whose sodium salt, Beraprost Sodium, is now commercially available as an anti-platelet drug.[5] With regard to synthesis of Beraprost, synthetic method of its racemic mixture has been already described so far.[6] Synthetic method of optically active form of Beraprost is little described.[4] We synthesized each isomer of Beraprost in order to compare the biological activity of 4 isomers. In this report we here disclose the results of its study on the synthesis of



PGI_2

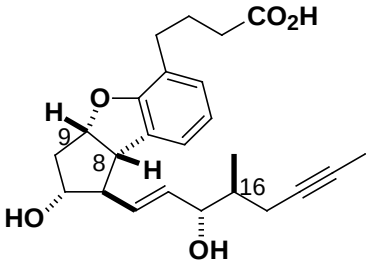


1 5,6,7-trinor-4,8-inter-*m*-phenylene PGI_2

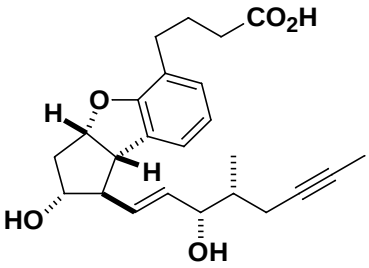


2 R=H : Beraprost
3 R=Na : Beraprost sodium

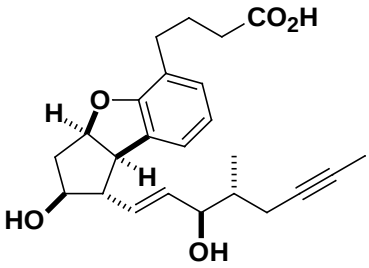
Figure 1. PGI_2 and its derivatives



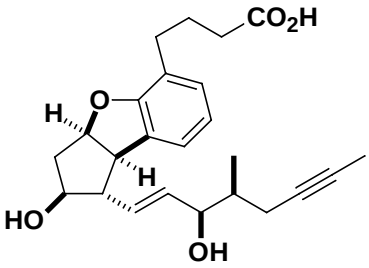
(8*S*,9*S*,16*S*)-form **5**



(8*S*,9*S*,16*R*)-form **6**



(8*R*,9*R*,16*R*)-form **7**



(8*R*,9*R*,16*S*)-form **8**

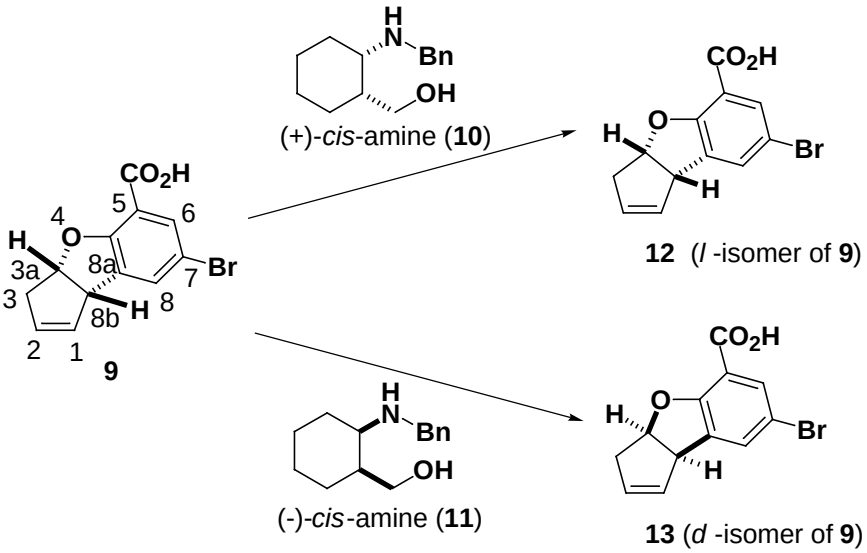
Figure 2. Beraprost as a mixture of 4 isomers

optically active *m*-phenylene PGI_2 derivative (**5 - 8**) (Figure 2).

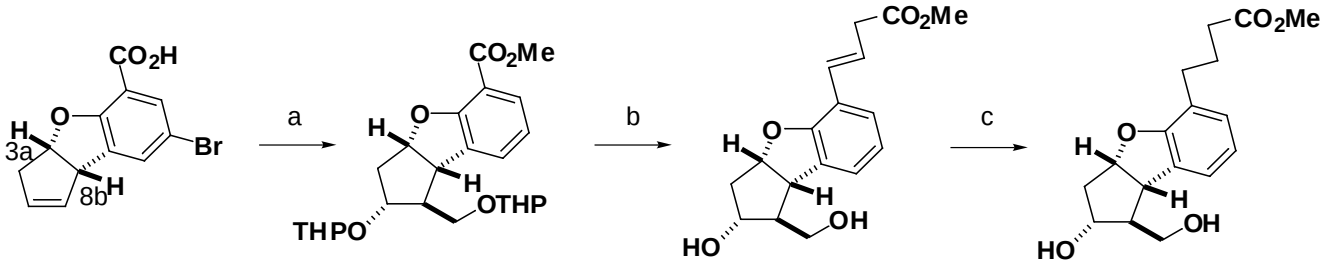
RESULTS AND DISCUSSION

We have already reported a synthetic method of optically active 3a,8b-*cis*-dihydro-3*H*-5-carboxy-7-bromocyclopenta[*b*]benzofurans (**1 2** and **1 3**) in practical scales by optical resolution of **9** with chiral amines (**1 0** and **11**), respectively (Scheme 1).[7]

We therefore adopted the bromo acids (**1 2** and **1 3**) as starting compounds for total synthesis of the Beraprost isomers. In order to introduce α- and ω-side chains to **1 2** and **1 3**, Wittig reaction and Prins reaction as key steps were examined to produce two important intermediates (**1 6 a** and **1 6 b**), respectively (Scheme 2); 1) Prins reaction; 2) hydrolysis; 3)



Scheme 1. Optical resolution of carboxylic acid (**9**)



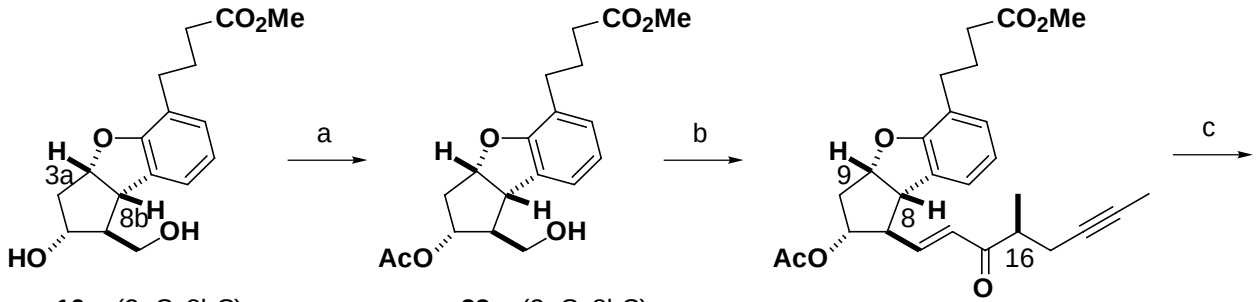
a: 1) trioxane, AcOH, H_2SO_4; 2) 10 N aq. NaOH ; 3) H_2, 10% Pd/C; 4) MeOH; 5) DHP, *p*-TsOH; b: 1) LAH; 2) MnO_2; 3) $Ph_3P^+CH_2CH_2CO_2H \cdot Br^-$, $MeS(=O)CH_2Na$; CH_2N_2 or MeI; 4) conc. HCl; c: H_2, 10% Pd/C

Scheme 2. Synthetic route of optically active diols (**16a** and **16b**) (The structure of this Scheme indicates the case of (3a*S*, 8b*S*)-form.)

hydrogenolysis; 4) methyl esterification; 5) protection of hydroxyl groups by THP; 6) reduction of ester into alcohol; 7) oxidation of the alcohol to aldehyde; 8) C-3 elongation by using Wittig reaction;[8] 9) deprotection of protective groups; 10) hydrogenation.

Thus obtained diols (**16a** and **16b**) were converted into acetates (**23a** and **23b**) by tritylation of primary hydroxyl group, followed by acetylation of secondary hydroxyl group and successive deprotection of trityl group (Scheme 3).

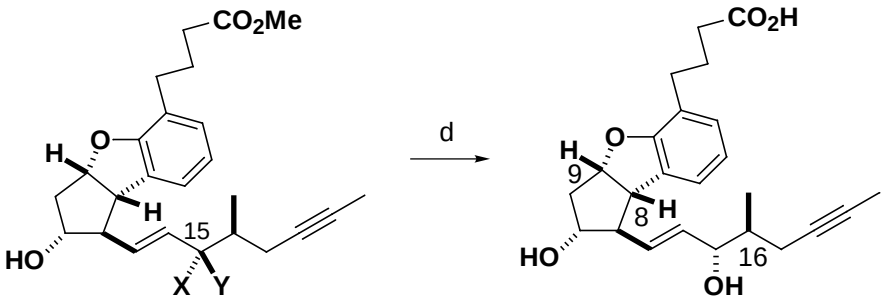
At the next step, *d*-isomer and *l*-isomer of Wadsworth reagent were necessary as starting materials of ω-side chain. The *d*-isomer (**19**) and *l*-isomer (**22**) of Wadsworth reagent were derived from (-)-2-methyl-4-hexynic acid (**17**) and (+)-2-methyl-4-hexynic acid (**20**) by met-



16a: (3a*S*, 8b*S*)
16b: (3a*R*, 8b*R*)

23a: (3a*S*, 8b*S*)
23b: (3a*R*, 8b*R*)

24a: (8*S*, 9*S*, 16*S*)
24b: (8*S*, 9*S*, 16*R*)
24c: (8*R*, 9*R*, 16*R*)
24d: (8*R*, 9*R*, 16*S*)



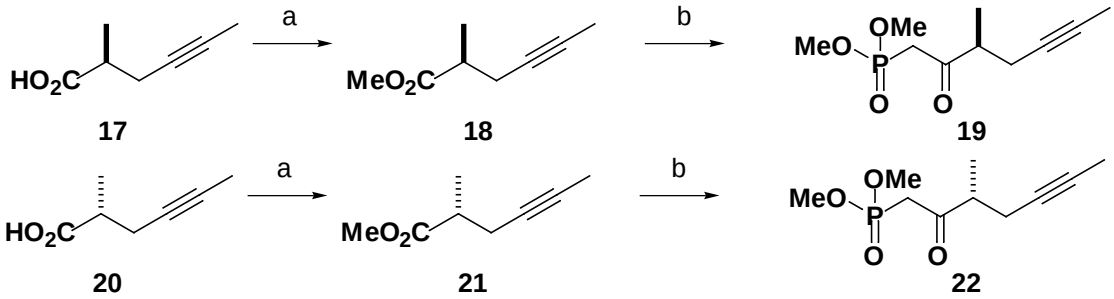
25a: X=OH, Y=H, (8*S*, 9*S*, 16*S*)
25b: X=OH, Y=H, (8*S*, 9*S*, 16*R*)
25c: X=OH, Y=H, (8*R*, 9*R*, 16*R*)
25d: X=OH, Y=H, (8*R*, 9*R*, 16*S*)

26a: X=H, Y=OH, (8*S*, 9*S*, 16*S*)
26b: X=H, Y=OH, (8*S*, 9*S*, 16*R*)
26c: X=H, Y=OH, (8*R*, 9*R*, 16*R*)
26d: X=H, Y=OH, (8*R*, 9*R*, 16*S*)

5: (8*S*, 9*S*, 16*S*)
6: (8*S*, 9*S*, 16*R*)
7: (8*R*, 9*R*, 16*R*)
8: (8*R*, 9*R*, 16*S*)

a: 1) TrCl, Et_3N; 2) Ac_2O, Py; 3) HCl; b: 1) DMSO, DCC, TFA, Py; 2) Wadsworth reagent, NaH; c: 1) $NaBH_4$, $CeCl_3 \cdot 7H_2O$; 2) MeONa; d: 2 N aq. NaOH

Scheme 3. Synthesis of optically active Beraprost (This Scheme indicates the case of (8*S*, 9*S*, 16*S*)-isomer.)

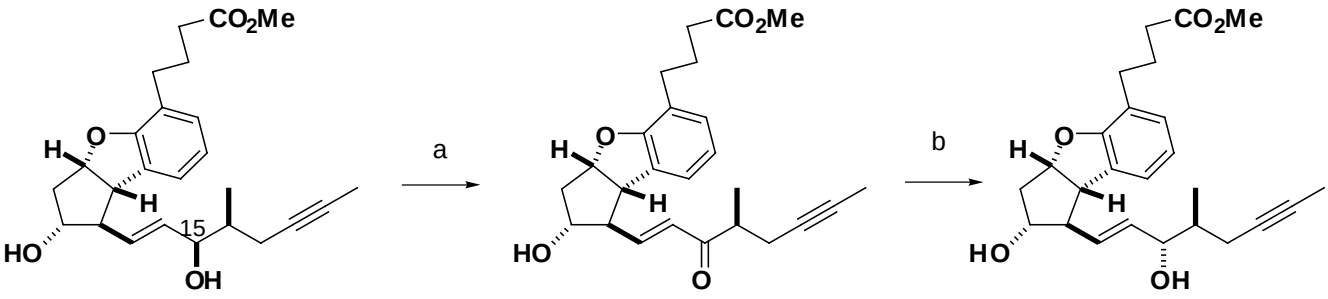


a: MeOH, H_2SO_4 or CH_2N_2; b: $MeP(=O)(OMe)_2$, *n*-BuLi

Scheme 4. Synthesis of optically active ω-side chain

hyl esterification and successive reaction with anion of dimethyl methylphosphonate, respectively (Scheme 4).[9]

The acetate (**23a**) described above was in turn condensed with chiral Wadsworth reagents (**19** and **22**) to yield 2 isomer forms, that is to say, (8*S*, 9*S*, 16*S*)-form (**24a**) and (8*S*, 9*S*, 16*R*)-form (**24b**), respectively (Scheme 3). The acetate (**23b**) was similarly condensed with chiral Wadsworth reagents (**22** and **19**) to yield 2 isomer forms, that is to say, (8*R*, 9*R*, 16*R*)-form (**24c**) and (8*R*, 9*R*, 16*S*)-form (**24d**), respectively. These isomers were converted into 15 α-isomers (**25a-d**) and 15 β-isomers (**26a-d**) of the corresponding methyl ester by 1,2-reduction using $CeCl_3 \cdot 7H_2O$ and $NaBH_4$ in MeOH,[10] followed by methanolysis. The obtained 15 β-isomers (**26a-d**) were respectively converted into 15 α-isomers (**25a-d**) by oxidation using MnO_2, followed by reduction (Scheme 5). Each 15 α-isomer (**25a-d**) was hydrolyzed into the carboxylic acid (**5**-**8**) (Scheme 3).



26a-26d **25a-25d**

a: MnO_2; b: $NaBH_4$, $CeCl_3 \cdot 7H_2O$

Scheme 5. Conversion of 15 β-isomers into 15 α-isomers (This Scheme indicates the case of (8*S*, 9*S*, 16*S*)-isomer.)

Finally, these stereoisomers were assayed for inhibition of platelet aggregation. The effect was tested in platelet-rich plasma (PRP) obtained from humans and against adenosine diphosphate (ADP, 2.5-10 μM)-induced aggregation (Table 1). By this assay, (8*S*, 9*S*, 16*S*)-isomer (**5**) was found to be most active isomer.

SUMMARY

The optical isomers of *m*-phenylene PGI_2 derivative, Beraprost, were synthesized by chiral *m*-phenylene mother skeleton and chiral Wadsworth reagent. Both of the starting materials

Table 1. Anti platelet activity of 4 isomers

compound [a)]	IC_{50} (nM)	activity ratio compared with Beraprost sodium
Beraprost sodium	5.25	1
(8*S*, 9*S*, 16*S*)-isomer	1.19	4.4
(8*S*, 9*S*, 16*R*)-isomer	21.3	0.25
(8*R*, 9*R*, 16*R*)-isomer	233	0.023
(8*R*, 9*R*, 16*S*)-isomer	1554	0.0034

a) Each optical isomer was evaluated as its sodium salt.

in condensation were derived from the two chiral carboxylic acids. The C-3 elongation in α-side chain of chiral *m*-phenylene mother skeleton was accomplished by using Wittig reaction.

ACKNOWLEDGEMENT

We gratefully acknowledge the late Dr. K. Ohno for his leadership and passion. And we would like to thank Dr. T. Tajima, Ms. M. Kajita, Mr. Y. Hosono, and Mr. R. Hayashi for analytical support.

EXPERIMENTAL

General. ^{1}H NMR spectra of $CDCl_3$ solution were recorded with JEOL GX-270 spectrometer at 270 MHz. IR spectra were recorded with Shimazu IR-400 spectrophotometer. MS spectra were recorded with Hitachi RML 7-M or JEOL JMS D-300 spectrometer. Melting points were determined on a Yanaco MP-S3 melting point apparatus and are uncorrected. Analytical TLC was performed with Merck precoated (0.25 mm) silica gel plates. Optical rotations were recorded with JEOL DIP-140 polarimeter at 20℃. The HPLC purity of **5**, **6**, **7**, and **8** was determined by measurement of the sample obtained by treatment of their sodium salt with diazomethane. HPLC condition: chiral HPLC column YMC AK03 (4 mm I.D.×25 cm); EtOH/Hexane/H_2O = 2/100/0.01; detection by 280 nm; flow rate 1.0 mL/min. The peaks of methyl ester (**25a**, **25b**, **25c**, and **25d**) were detected at retention time = 47.5 min, 49.9 min, 54.8 min, and 57.0 min, respectively. The purity of each isomer was found to be more

than 98%.

Methyl ester (14a)

A mixture of the carboxylic acid (**12**)[7] (*l*-isomer, 300 g, 1.07 mol, >99.5% e.e.), trioxane (192.3 g, 2.13 mol), acetic acid (1302 g, 21.7 mol), and concentrated sulfuric acid (98%, 210 g, 2.10 mol) was refluxed at 80℃ for 4.5 h. The mixture was cooled below 50℃ and neutralized with $NaHCO_3$ (189 g, 2.25 mol). The acetic acid in the reaction mixture was removed under reduced pressure.

The obtained residue was dissolved in a mixture of MeOH (3 L) and H_2O (0.5 L) and treated with 10 N NaOH aqueous solution (1068 mL, 10.68 mol). The solution was refluxed for 2 h. The solution was filtered through celite and the insoluble solid was washed with 70% MeOH aqueous solution (1 L). The combined filtrates were acidified by addition of concentrated HCl (1 L) and the organic solvent in the filtrate was evaporated. EtOAc (2 L) was added and the organic layer was separated. The organic layer was washed with H_2O 3 times and each aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated to give an oil (421 g).

The obtained residue was dissolved in MeOH (3.5 L) and treated with 10% Pd/C (60 g). The mixture was stirred under H_2 atmosphere. After dilution with MeOH (5 L), the reaction mixture was refluxed for 12 h and then neutralized with $NaHCO_3$ (89.6 g, 1.07 mol). After stirring for 30 min, filtration through celite and concentration of the filtrate gave an oil (373 g). The obtained residue was dissolved in THF (3 L) and treated with dihydropyran (359.2 g, 4.27 mol) and *p*-toluenesulfonic acid (10.0 g, 52.6 mmol). The solution was stirred for 2 h and neutralized with pyridine (4.22 g, 53.4 mmol). The resulting solution was concentrated and the obtained residue was dissolved in a mixture of EtOAc (2 L) and H_2O (0.5 L). The organic layer was separated and washed with brine 3 times. Each aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and evaporated. The same procedure was repeated 2 times by using the carboxylic acid (**12**) (300 g, 1.07 mol).

The combined residues were briefly chromatographed on SiO_2 (5 kg), eluting with a mixture of cyclohexane and EtOAc to yield an oil (646 g). The obtained oil was further chromatographed on SiO_2 (Merck Art 13905, 2 kg), eluting with a mixture of cyclohexane and EtOAc to give pure oily methyl ester (**14a**) (560 g, 40.2%): ^{1}H-NMR δ 1.10-1.95 (12H, m), 2.05-2.72

(3H, m), 3.32-4.27 (11H, m), 4.54-4.70, 4.73-5.11 (2H, m), 5.27-5.41, 5.59-5.68 (1H, m), 6.81-6.92 (1H, m), 7.32-7.47 (1H, m), 7.65-7.78 (1H, m); IR(neat) 2944, 1726, 1714, 1447, 1135, 1035 cm^{-1}; $[\alpha]_D$= +95.18° (c 1.0, EtOH); LRMS m/z 432 (M^+); HRMS calcd for $C_{24}H_{32}O_7$ 432.2148, found 432.2129.

Preparation of triphenyl-2-carboxyethylphosphonium bromide

A solution of 3-bromopropionic acid (61.2 g, 0.400 mol) and triphenylphosphine (110.2 g, 0.420 mol) in MeCN (300 mL) was refluxed for 26 h. To the solution was added ether (400 mL) and the mixture was cooled in a refrigerator for 1 d. The precipitate was filtered out, washed with MeCN (83 g) and ether (100 g), and dried under reduced pressure to yield phosphonium salt (149 g, 89.7%). The same procedure was repeated 4 times by using 3-bromopropionic acid (183.6 g, 1.2 mol) to give phosphonium salt (1660 g, 83.3%).

C-3 Elongation of methyl ester (14a)

The methyl ester (**14a**) (356.0 g, 0.823 mol) was dissolved in THF (3 L) and 1.5 M $LiAlH_4$-THF solution (520 mL, 0.78 mol) was slowly added during 1 h at -20～-10℃. The solution was treated with brine (50 mL) below 0℃ and then $MgSO_4$ (150 g) was added to the mixture. The resulting suspension was stirred for 30 min and filtered through celite. The insoluble solid was washed with THF 5 times and the combined filtrates were concentrated to give an oil (329.8 g).

A part of the obtained residue (283.8g) was dissolved in CH_2Cl_2 (1.8 L) and treated with MnO_2 (610 g, 7.02 mol). The mixture was stirred at rt for 15 h and filtered through celite. The insoluble solid was washed with EtOAc and the filtrate was evaporated below 40℃ to yield aldehyde as an oil (274.0 g).

Triphenyl-2-carboxyethylphosphonium bromide (706.8 g, 1.70 mol) was dissolved in DMSO (2.1 L) and treated with 2.6 M sodium salt of DMSO in DMSO (1309 mL, 3.40 mol) below 10 ℃. To the solution was added the aldehyde (274.0 g, *ca*. 0.68 mol) in THF solution (800 mL) below 10℃ and the resulting solution was heated at 50℃ for 18 h. The solution was cooled in an ice bath and treated with iodomethane (500 g, 3.52 mol) below 10℃. The solution was stirred at rt for 14 h. To the solution were added H_2O (1.5 L) and oxalic acid (53.6 g, 0.595 mol) and the mixture was stirred for 10 min. The solution was extracted with EtOAc 3 times and each organic layer was washed with brine. The combined organic layers were dried

over $MgSO_4$ and concentrated to give an oil (323 g). The residue was purified by column chromatography (SiO_2, 10-25 μm, 2 kg, EtOAc/cyclohexane = 1/6) to give THP-protected butenoate derivative (252.2 g, 75.4%) as an oil.

A solution of THP-protected butenoate derivative (252.0 g, 0.533 mol) in MeOH (1.5 L) was treated with concentrated HCl (0.5 mL) and heated at 50～60℃ for 1 h. To the solution was added $NaHCO_3$ (510 mg, 6.07 mmol) and the mixture was concentrated. The residue was dissolved in MeOH (1.5 L) and the resulting solution was treated with concentrated HCl (0.5 mL). The solution was heated at 50-60℃ for 1 h again. To the mixture was added $NaHCO_3$ (550 mg, 6.55 mmol) and the suspension was concentrated. To the residue were added EtOAc (500 mL) and H_2O (50 mL). The aqueous layer was separated and extracted with EtOAc 3 times. Each organic layer was washed with brine. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (EtOAc/cyclohexane = 1/3 - EtOAc) to give dihydroxybutenoate derivative (**15a**) (158.0 g, 97.4%). The pure dihydroxybutenoate derivative (**15a**) was recrystallized from a mixture of EtOAc and *n*-hexane to give a white crystal (138.8 g, 85.6%); mp 72.0-74.0℃; ^{1}H-NMR δ 1.98-2.25 (3H, m), 2.42 (1H, br s), 2.52-2.68 (1H, m), 3.25 (2H, d, *J* = 5.4 Hz), 3.38 (1H, t, *J* = 8.3 Hz), 3.71 (3H, s), 3.70-3.82 (1H, m), 3.85-3.99 (1H, m), 4.02-4.18 (1H, m), 5.08-5.20 (1H, m), 6.39-6.57 (2H, m), 6.81 (1H, t, *J* = 7.6 Hz), 7.03 (1H, d, *J* = 6.4 Hz), 7.15 (1H, d, *J* = 7.3 Hz); IR(KBr) 3200, 2930, 1735, 1442, 1230, 1142, 1065, 1030 cm^{-1}; $[\alpha]_D$ = +93.03° (c 1.2, EtOH); LRMS m/z 304 (M^+); HRMS calcd for $C_{17}H_{20}O_5$ 304.1311, found 304.1323.

Dihydroxybutanoate derivative (16a)

A solution of dihydroxybutenoate derivative (**15a**) (137.8 g, 0.453 mol) in MeOH (1.5 L) was stirred under H_2 atmosphere in the presence of 10% Pd/C (wet 50%, 22 g) for 3 h. The mixture was filtered and the obtained filtrate was evaporated to give an oil (135.3 g). The residue was recrystallized from a mixture of EtOAc (110 g) and *n*-hexane (45 g) to yield dihydroxybutanoate derivative (**16a**) (119 g, 85.7%): mp 61.0-63.0℃; ^{1}H-NMR δ 1.58 (2H, br s), 1.72-2.40 (6H, m), 2.48-2.70 (3H, m), 3.40 (1H, t, *J* = 7.9 Hz), 3.64 (3H, s), 3.70-3.85 (1H, m), 3.88-4.03 (1H, m), 4.05-4.19 (1H, m), 5.05-5.18 (1H, m), 6.77 (1H, t, *J* = 7.4 Hz), 6.94 (1H, d, *J* = 6.9 Hz), 7.01 (1H, d, *J* = 7.3 Hz); IR(KBr) 3230, 2950, 1730, 1445, 1348, 1255, 1175, 1060, 1030 cm^{-1}; $[\alpha]_D$ = +25.29° (c 1.2, EtOH); LRMS m/z 306(M^+); HRMS calcd for $C_{17}H_{22}O_5$

306.1467, found 306.1469.

Acetate (**23a**)

A solution of dihydroxybutanoate derivative (**16a**) (100 g, 0.326 mol), trityl chloride (137.5 g, 0.493 mol), and triethylamine (137 mL, 0.983 mol) in THF (600 mL) was refluxed for 5.5 h. The reaction mixture was cooled below 50℃ and treated with acetic anhydride (125 mL, 1.32 mol) and pyridine (107 mL, 1.32 mol). After reflux for 6 h followed by cooling below 10 ℃, the resulting mixture was treated with 2.95 N HCl-MeOH solution (700 mL, 2.07 mol) below 30℃ and stirred at 30℃ for 2 h. To the solution was added $NaHCO_3$ (21.6 g, 0.257 mol) and the resulting suspension was concentrated. The obtained residue was dissolved in a mixture of EtOAc and H_2O and the organic layer was separated. The aqueous layer was extracted with EtOAc 3 times and each organic layer was washed with 1 N HCl (300 mL) and brine (750 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (Merck Art 13905, 2 kg, EtOAc / cyclohexane = 2/3) to give acetate (**23a**) (93.5 g, 82.2%); ^{1}H-NMR δ 1.80 (3H, s), 1.83-1.99 (2H, m), 2.12-2.38 (4H, m), 2.47-2.70 (4H, m), 3.66 (3H, s), 3.60-3.76 (3H, m), 5.07 (1H, q, *J* = 5.5 Hz), 5.13-5.23 (1H, m), 6.77 (1H, t, *J* = 7.3 Hz), 6.93 (1H, d, *J* = 7.3 Hz), 7.03 (1H, d, *J* = 7.3 Hz); IR (neat) 3400, 2955, 1730, 1452, 1365, 1240, 1040 cm^{-1}; $[\alpha]_D$ = +25.94° (c 1.2, EtOH); LRMS m/z 348 (M^+); HRMS calcd for $C_{19}H_{24}O_6$ 348.1572, found 348.1542.

Methyl ester (**14b**)

A mixture of the carboxylic acid (**13**)[7] (*d*-isomer, 300 g, 1.07 mol, >99.5% e.e.), trioxane (192.3 g, 2.13 mol), acetic acid (1220 g, 21.3 mol), and concentrated sulfuric acid (98%, 116 mL, 2.13 mol) was refluxed at 80℃ for 7 h. The reaction solution was cooled below 50℃ and neutralized with $NaHCO_3$ (197 g, 2.34 mol). The acetic acid in the reaction suspension was removed under reduced pressure.

The obtained residue was dissolved in a mixture of MeOH (3 L) and H_2O (0.5 L) and treated with 10 N NaOH (1120 mL, 11.2 mol). The solution was refluxed for 2 h. The solution was filtered through celite and the insoluble solid was washed with 70% MeOH aqueous solution (1 L). The combined filtrates were acidified by addition of concentrated HCl (0.5 L) and the organic solvent was evaporated. EtOAc (2 L) was added and the organic layer was separated. The organic layer was washed with H_2O 3 times and each aqueous layer was extracted

with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated to give an oil (473 g).

The obtained residue was dissolved in MeOH (3 L) and treated with 10% Pd/C (60 g). The mixture was stirred under H_2 atmosphere. After dilution with MeOH (5 L), the reaction mixture was refluxed for 15 h and then neutralized with $NaHCO_3$ (89.6 g, 1.07 mol) After stirring for 30 min, filtration through celite and concentration of the filtrate gave an oil (394 g).

The obtained residue was dissolved in THF (3 L) and treated with dihydropyran (359.2 g, 4.27 mol) and *p*-toluenesulfonic acid (10.1 g, 53.1 mmol). The solution was stirred for 2 h and neutralized with pyridine (4.2 g, 53.1 mmol). The resulting solution was concentrated and the obtained residue was dissolved in a mixture of EtOAc (2 L) and H_2O (0.5 L). The organic layer was separated and washed with brine 3 times. Each aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and evaporated.

The same procedure was repeated 2 times by using the carboxylic acid (**13**) (300 g, 1.07 mol).

The combined residues were briefly chromatographed on SiO_2 (5 kg), eluting with a mixture of cyclohexane and EtOAc to yield an oil (684 g). The obtained oil was further chromatographed on SiO_2 (Merck Art 13905, 2 kg), eluting with a mixture of cyclohexane and EtOAc to give pure oily methyl ester (**14b**) (604.8 g, 43.6%): ^{1}H-NMR δ 1.10-1.95 (12H, m), 2.05-2.65 (3H, m), 3.30-4.25 (11H, m), 4.48-4.72 (2H, m), 5.25-5.45 (1H, m), 6.85 (1H, t, *J* = 7.6 Hz), 7.30-7.49 (1H, m), 7.71 (1H, d, *J* = 7.9 Hz); IR(neat) 2941, 1728, 1713, 1446, 1292, 1136, 1036 cm^{-1}; $[\alpha]_D$ = -95.83° (c 1.0, EtOH); LRMS m/z 432 (M^+); HRMS calcd for $C_{24}H_{32}O_7$ 432.2148, found: 432.2150.

C-3 Elongation of methyl ester (14b)

The methyl ester (**14b**) (169 g, 0.391 mol) was dissolved in THF (1.5 L) and 1.5 M $LiAlH_4$-THF solution (250 mL, 0.375 mol) was slowly added during 1 h at -20～-10℃. The solution was treated with brine (50 mL) below 0℃ and $MgSO_4$ (150 g) was added to the mixture. The resulting suspension was stirred for 30 min and filtered through celite. The insoluble solid was washed with THF 5 times and the combined filtrates were concentrated to give an oil (160.3 g).

The obtained residue (160.3 g) was dissolved in CH_2Cl_2 (1.2 L) and treated with MnO_2

(344.8 g, 3.97 mol). The mixture was stirred at rt for 14 h and filtered through celite. The insoluble solid was washed with EtOAc and the filtrate was evaporated below 40℃ to yield aldehyde as an oil (159.2 g).

Triphenyl-2-carboxyethylphosphonium bromide (415.3 g, 1.00 mol) was dissolved in DMSO (1.2 L) and treated with 2.6 M sodium salt of DMSO in DMSO (720 mL, 1.87 mol) below 10 ℃. To the solution was added the aldehyde (159.2 g, *ca.* 0.39 mol) in THF solution (500 mL) below 10℃ and the resulting solution was refluxed for 28 h. The solution was washed with THF / cyclohexane (1/6) 3 times and the aqueous layer was acidified by addition of oxalic acid (200 g, 2.22 mol). The aqueous layer was extracted with EtOAc (1 L × 4) and each organic layer was washed with brine. The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was treated with 1 M CH_2N_2 in ether solution in an ice bath. The excess CH_2N_2 was decomposed by addition of AcOH and the solution was concentrated to give an oil (261.1 g). The residue was purified by column chromatography (SiO_2, 10 - 25 μm, 2 kg, EtOAc/cyclohexane = 1/5) to give THP-protected butenoate derivative (159.2 g, 86.2%).

A solution of THP-protected butenoate derivative (159.2 g, 0.337 mol) in MeOH (1 L) was treated with concentrated HCl (0.5 mL) and heated at 50-60℃ for 1 h. To the solution was added $NaHCO_3$ (510 mg, 6.07 mmol) and the mixture was concentrated. The residue was dissolved in MeOH (1 L) and the resulting solution was treated with concentrated HCl (0.5 mL). The solution was heated at 50-60℃ for 1 h again. To the mixture was added $NaHCO_3$ (550 mg, 6.55 mmol) and the suspension was concentrated. The residue was dissolved in EtOAc (300 mL) and the solution was washed with H_2O (30 mL). The aqueous layer was extracted with EtOAc 3 times and each organic layer was washed with brine. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue (107 g) was purified by column chromatography (EtOAc/cyclohexane = 1/5 - EtOAc) to give dihydroxybutenoate derivative (**15b**) (78.2 g, 76.3%). The pure dihydroxybutenoate derivative (**15b**) was recrystallized from a mixture of EtOAc and *n*-hexane to give a white crystal (69.9 g, 68.2%); mp 73.5-74.5℃; ^{1}H-NMR δ 1.98-2.14 (2H, m), 2.37 (1H, br s), 2.53-2.64 (2H, m), 3.25 (2H, d, *J* = 5.5 Hz), 3.37 (1H, t, *J* = 8.2 Hz), 3.70 (3H, s), 3.70-3.80 (1H, m), 3.82-3.97 (1H, m), 4.00-4.15 (1H, m), 5.08-5.20 (1H, m), 6.38-6.55 (2H, m), 6.80 (1H, t, *J* = 7.3 Hz), 7.03 (1H, d, *J*

= 7.3 Hz), 7.15 (1H, d, *J* = 7.3 Hz); IR(KBr) 3200, 2930, 1738, 1445, 1228, 1142, 1065, 1030 cm^{-1}; $[\alpha]_D$ = -98.69° (c 1.0, EtOH); LRMS m/z 304 (M^+); HRMS calcd for $C_{17}H_{20}O_5$ 304.1311, found 304.1317.

D**ihydroxybutanoate derivative** (**16b**)

A solution of dihydroxybutenoate derivative (**15b**) (66.4 g, 0.218 mol) in MeOH (0.7 L) was stirred under H_2 atmosphere in the presence of 10% Pd/C (wet 50%, 18 g) for 4 h. The mixture was filtered and the obtained filtrate was evaporated to give an oil. The residue was recrystallized from a mixture of EtOAc and *n*-hexane to yield dihydroxybutanoate derivative (**16b**) (58.9 g, 88.1%); mp 59.0-61.0℃; ^{1}H-NMR δ 1.83-2.15 (4H, m), 2.32 (2H, t, *J* = 7.6 Hz), 2.48-2.70 (4H, m), 2.84 (1H, br s), 3.39 (1H, t, *J* = 8.2 Hz), 3.64 (3H, s), 3.67-3.78 (1H, m), 3.83-3.95 (1H, m), 4.01-4.13 (1H, m), 5.04-5.14 (1H, m), 6.77 (1H, t, *J* = 7.3 Hz), 6.94 (1H, d, *J* = 7.3 Hz), 7.01 (1H, d, *J* = 7.3 Hz); IR(KBr) 3230, 2950, 1733, 1445, 1350, 1255, 1180, 1065 cm^{-1}; $[\alpha]_D$ = -27.23° (c 1.0, EtOH); LRMS m/z 306 (M^+); HRMS calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1489.

Acetate (**23b**)

A solution of dihydroxybutanoate derivative (**16b**) (104 g, 0.339 mol), trityl chloride (142.9 g, 0.513 mol), and triethylamine (143 mL, 1.03 mol) in THF (500 mL) was refluxed for 2.5 h. The reaction mixture was cooled below 50℃ and treated with acetic anhydride (130 mL, 1.38 mol) and pyridine (111 mL, 1.37 mol). The reaction mixture was refluxed for 3 h and cooled below 10℃. To the mixture was added 3.5 N HCl-MeOH solution (630 mL, 2.21 mol) below 30℃ and the resulting mixture was stirred at 30℃ for 1 h. To the mixture was added $NaHCO_3$ (35 g, 0.42 mol) and the resulting mixture was concentrated. The residue was dissolved in a mixture of EtOAc and H_2O and the organic layer was separated. The aqueous layer was extracted with EtOAc 3 times and each organic layer was washed with 1 N HCl (300 mL) and brine (750 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (Merck Art 13905, 2 kg, EtOAc/cyclohexane = 2/3) to give acetate (**23b**) (89.5 g, 75.8%) as an oil. The same procedure was repeated by using dihydroxybutanoate derivative (**16b**) (25 g, 0.082 mol) to yield acetate (**23b**) (22.3 g, 78 %); ^{1}H-NMR δ 1.80 (3H, s), 1.83-1.99 (2H, m), 2.12-2.38 (4H, m), 2.47-2.70 (4H, m), 3.66 (3H, s), 3.60-3.76 (3H, m), 5.07 (1H, q, *J* = 5.9 Hz), 5.13-5.23 (1H, m),

6.77 (1H, t, *J* = 7.3 Hz), 6.94 (1H, d, *J* = 7.3 Hz), 7.03 (1H, d, *J* = 7.3 Hz); IR (neat) 3500, 2960, 1730, 1450, 1365, 1240, 1030 cm^{-1}; $[\alpha]_D$ = -25.94° (c 1.2, EtOH); LRMS m/z 348 (M^+); HRMS calcd for $C_{19}H_{24}O_6$ 348.1572, found: 348.1524.

Wadsworth reagent (19)

To a solution of (-)-2-methylhexynic acid (**17**)[9] (145 g, 1.15 mol, 99.9% e.e.) in MeOH (2.5 L) was added concentrated sulfuric acid (5 mL) and the solution was refluxed for 24 h. The solution was allowed to stand at rt and treated with $NaHCO_3$ (10 g, 0.12 mol). The mixture was concentrated to give residue (155.4 g). To the residue were added EtOAc (700 mL) and $MgSO_4$ (5 g). The mixture was filtered and the filtrate was treated with 1 M CH_2N_2 solution in ether (50 mL, 50 mmol) in order to esterify the unreacted acid. Distillation gave methyl ester (**18**) (128.6 g, 79.7%); bp 65-68℃/11-12 mmHg.

Dimethyl methylphosphonate (372.3 g, 3.00 mol) was dissolved in THF (2 L). To the solution was added 1.56 M BuLi hexane solution (1923 mL, 3.00 mol) during 1.5 h below -50℃. The solution was stirred for 30 min and cooled below -60℃. To the solution was added a solution of methyl ester (**18**) (130 g, 0.927 mol) in THF (300 mL) during 45 min. The solution was stirred for 1 h and the temperature of the solution was raised to -20℃. To the solution were added EtOAc (180 mL) and H_2O (400 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc 3 times and each organic layer was washed with brine. The combined organic layers were dried over $MgSO_4$ and concentrated to give an oil (203 g). Distillation gave Wadsworth reagent (**19**) (181.4 g, 84.3%); bp 110-118℃/0.05-0.06 mmHg. The pure **19** was analyzed *via* capillary GC: 3 mm×15 m Dexil 300GC 5wt% Uniport - UH 80-100 mesh, 12.5 mL/min, 150-230℃/10℃min^{-1}; t_R = 8.1 min, GC purity 97.6%. ^{1}H-NMR δ 1.20 (3H, d, *J* = 7.3 Hz), 1.76 (3H, t, *J* = 2.4 Hz), 2.22-2.47 (2H, m), 2.92 (1H, dt, *J* = 6.7, 6.7 Hz), 3.17 (1H, dd, *J* = 20.1, 14.0 Hz), 3.25 (1H, dd, *J* = 20.1, 14.0 Hz), 3.78 (6H, d, *J* = 21.6 Hz); IR(neat) 2957, 2921, 1713, 1458, 1259, 1183, 1030, 810 cm^{-1}; $[\alpha]_D$ = +33.4° (c 10.0, EtOH); LRMS m/z 232 (M^+); HRMS calcd for $C_{10}H_{17}O_4P$ 232.0864, found 232.0887.

Wadsworth reagent (22)

A solution of (+)-2-methylhexynic acid (**20**)[9] (140 g, 1.11 mol, 99.6% e.e.) in EtOAc (800 mL) was treated with 1 M CH_2N_2 ether solution (1.2 L, 1.2 mol) below 10℃. Distillation gave methyl ester (**21**) (146 g, 93.8%); bp 63-65℃/10 mmHg.

Dimethyl methylphosphonate (372.3 g, 3.00 mol) was dissolved in THF (2 L). To the solution was added 1.56 M BuLi hexane solution (1923 mL, 3.00 mol) during 2 h below -50℃. The solution was stirred for 30 min and cooled below -60℃. To the solution was added a solution of methyl ester (**21**) (146 g, 1.04 mol) in THF (300 mL) during 45 min. The solution was stirred for 1 h and the temperature of the solution was raised to -20℃. To the solution were added EtOAc (180 mL) and H_2O (450 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc 3 times and each organic layer was washed with brine. The combined organic layers were dried over $MgSO_4$ and concentrated to give an oil (258 g). Distillation gave Wadsworth reagent (**22**) (218.3 g, 90.4%); bp 115-120℃/0.03-0.07 mmHg. The pure **22** was analyzed under the condition described above: GC purity 99.0%. ^{1}H-NMR δ 1.20 (3H, d, *J* = 6.7 Hz), 1.76 (3H, t, *J* = 2.4 Hz), 2.22-2.47 (2H, m), 2.92 (1H, dt, *J* = 6.7, 6.7 Hz), 3.17 (1H, dd, *J* = 20.1, 14.0 Hz), 3.25 (1H, dd, *J* = 20.1, 14.0 Hz), 3.80 (6H, d, *J* = 21.6 Hz); IR(neat) 2957, 2922, 1714, 1458, 1259, 1184, 1030, 810 cm^{-1}; $[\alpha]_D$ = -32.5° (c 10.1, EtOH); LRMS m/z 232 (M^+); HRMS calcd for $C_{10}H_{17}O_4P$ 232.0864, found 232.0892.

(8*S*,9*S*,16*S*)-Enone (**24a**)

To a solution of acetate (**23a**) (60 g, 0.172 mol) and *N,N'*-dicyclohexylcarbodiimide (42.7 g, 0.207 mol) in THF (300 mL) were added DMSO (184 mL, 2.59 mol), trifluoroacetic acid (2.6 mL, 33.7 mmol), and pyridine (2.8 mL, 34.6 mmol). After stirring at rt for 10 h to give an aldehyde, the reaction mixture was cooled in an ice bath.

To a suspension of 60% NaH (8.96 g, 0.224 mol) in THF (200 mL) was added a solution of Wadsworth reagent (**19**) (53.6 g, 0.231 mol) in THF (100 mL) below 25℃. The solution was cooled in an ice bath. To the solution of sodium salt of Wadsworth reagent was added the reaction mixture of the aldehyde below 10℃. The resulting suspension was stirred for 3 h and treated with AcOH (13.4 mL, 0.234 mol). To the mixture was added cyclohexane (300 mL) and the insoluble solid was filtered off. The filtrate was concentrated and the resulting residue was dissolved in EtOAc. The organic layer was washed with brine 3 times and each brine layer was extracted with EtOAc. The combined organic layers were dried over MgSO4 and concentrated. The same procedure was repeated by using acetate (**23a**) (54 g, 0.155 mol) and the obtained residue was combined with the residue described above. The residue was purified by column chromatography (EtOAc/cyclohexane = 1/5) to give (8*S*,9*S*,16*S*)-

enone (**24a**) (137.0 g, 92.7%) as an oil; ^{1}H-NMR δ 1.21 (3H, d, *J* = 7.0 Hz), 1.72-1.82 (6H, m), 1.88-2.03 (2H, m), 2.10-2.54 (5H, m), 2.55-2.72 (3H, m), 2.87-3.02 (2H, m), 3.68 (3H, s), 3.60-3.74 (1H, m), 5.01 (1H, q, *J* = 6.0 Hz), 5.20-5.29 (1H, m), 6.28 (1H, dd, *J* = 15.8, 1.1 Hz), 6.77 (1H, t, *J* = 7.3 Hz), 6.83 (1H, dd, *J* = 15.8, 8.4 Hz), 6.95 (1H, d, *J* = 7.3 Hz), 6.96 (1H, d, *J* = 7.3 Hz); IR(neat) 2950, 1735, 1455, 1370, 1235, 1040 cm^{-1}; $[\alpha]_D$ = +109.05° (c 10.0, EtOH); LRMS m/z 452 (M^+); HRMS calcd for $C_{27}H_{32}O_6$ 452.2196, found 452.2159.

(8*S*,9*S*,16*S*)-Methyl ester (**25a**)

To a solution of (8*S*,9*S*,16*S*)-enone (**24a**) (137 g, 0.303 mol) and $CeCl_3 \cdot 7H_2O$ (67.7 g, 0.182 mol) in MeOH (2.5 L) was added $NaBH_4$ (5.75 g, 0.152 mol). To the solution was added saturated $NaHCO_3$ aqueous solution (150 mL). The mixture was stirred for 1 h and filtered. The obtained filtrate was concentrated and the residue was treated with EtOAc and brine. The organic layer was separated and the aqueous layer was extracted with EtOAc 3 times. Each organic layer was washed with brine and combined. The organic layer was dried over $MgSO_4$ and concentrated to give an oil (134.2 g).

The residue was dissolved in MeOH (2 L) and treated with 4.85 M NaOMe (11.8 mL, 57.2 mmol). The solution was stirred at rt for 20 h and neutralized by addition of AcOH (4 mL, 70 mmol). The solution was concentrated and the residue was treated with a mixture of EtOAc (2 L) and H_2O (25 mL). The resulting solution was dried over $MgSO_4$ (50 g) and filtered. The filtrate was concentrated to give an oil (120.4 g). The residue was purified by column chromatography (EtOAc/cyclohexane = 2/3-2/1) to give (8*S*,9*S*,16*S*)-methyl ester (**25a**) (37.1 g, 29.7%) as a white crystal, its epimer at C-15 (**26a**) (48 g, 38%) as a white crystal, and a mixture of **25a** and **26a** (8.9 g, 7.1%).

(8*S*,9*S*,16*S*)-methyl ester (**25a**)

mp 83.0-85.0℃ (EtOAc/cyclohexane); ^{1}H-NMR δ 0.98 (3H, d, *J* = 6.6 Hz), 1.68-1.82 (4H, m), 1.82-2.02 (3H, m), 2.20-2.28 (2H, m), 2.28-2.42 (3H, m), 2.53-2.72 (3H, m), 3.07 (1H, br s), 3.32-3.50 (2H, m), 3.64 (3H, s), 3.80-3.91 (1H, m), 4.01 (1H, t, *J* = 7.3 Hz), 5.01-5.10 (1H, m), 5.48-5.70 (2H, m), 6.75 (1H, t, *J* = 7.5 Hz), 6.86-6.96 (2H, m); IR (KBr) 3580, 3420, 2970, 2920, 2880, 1715, 1435, 1250 cm^{-1}; $[\alpha]_D$ = +115.57° (c 1.0, EtOH); LRMS m/z 412 (M^+); HRMS calcd for $C_{25}H_{32}O_5$ 412.2250, found 412.2237.

its epimer at C-15 (**26a**)

mp 120.0-122.5℃ (EtOAc/cyclohexane); ^{1}H-NMR δ 1.01 (3H, d, *J* = 7.0 Hz), 1.72-1.85 (4H, m), 1.85-2.05 (3H, m), 2.05-2.25 (4H, m), 2.32 (2H, t, *J* = 7.5 Hz), 2.49 (1H, q, *J* = 7.3 Hz), 2.54-2.68 (3H, m), 3.48 (1H, t, *J* = 8.4 Hz), 3.65 (3H, s), 3.90-3.98 (1H, m), 4.23 (1H, t, *J* = 4.2 Hz), 5.05-5.14 (1H, m), 5.59-5.78 (2H, m), 6.76 (1H, t, *J* = 7.3 Hz), 6.90-6.99 (2H, m); IR (KBr) 3555, 3345, 2950, 2900, 1725, 1440, 1180 cm^{-1}; $[\alpha]_D$ = +60.76° (c 1.0, EtOH); LRMS m/z 412 (M^+); HRMS calcd for $C_{25}H_{32}O_5$ 412.2250, found 412.2249.

The obtained epimer at C-15 (**26a**) (41.8 g, 0.101 mol) was converted into (8*S*,9*S*,16*S*)-methyl ester (**25a**) by oxidation using MnO_2 (303.5 g, 3.49 mol) in CH_2Cl_2 (500 mL), followed by reduction using $CeCl_3 \cdot 7H_2O$ (22.8 g, 0.0612 mol) and $NaBH_4$ (1.91 g, 0.0505 mol) in MeOH (830 mL). The reaction mixture was worked up in the same procedure as described above and the obtained concentrate was chromatographed together with a mixture of **25a** and **26a** above-mentioned. The recycle process was repeated 4 times to give (8*S*,9*S*,16*S*)-methyl ester (**25a**) (80.9 g, 64.8%) in total.

(8*S*,9*S*,16*S*)-Carboxylic acid (5)

To a solution of (8*S*,9*S*,16*S*)-methyl ester (**25a**) (71 g, 0.172 mol) in MeOH (1.8 L) was added 2 N NaOH aqueous solution (260 mL, 0.52 mol) in an ice bath at such a rate that the temperature of the reaction solution was below 10℃. The solution was stirred at rt for 28 h. The solution was concentrated below 40℃ and the resulting residue was dissolved in H_2O (350 mL). The solution was washed with a mixture of ether and cyclohexane (1/1, 500 mL) and cooled below 10℃. The solution was slowly neutralized with citric acid monohydrate (43.7 g, 0.208 mol) and extracted with EtOAc 3 times. Each organic layer was washed with brine and combined. The organic layer was dried over $MgSO_4$ and concentrated to give 78 g. The residue was purified by column chromatography 2 times (1st: EtOAc/cyclohexane = 1/1～EtOAc containing 1% H_2O, 2nd: 2-propanol/*n*-hexane = 1/10). The obtained acid was dispersed in a mixture of EtOH (5 mL) and H_2O (100 mL) and freeze-dried to give (8*S*,9*S*,16*S*)-carboxylic acid (**5**) (32.6 g, 47.6%); mp 59.1-61.0℃; ^{1}H-NMR δ 0.98 (3H, d, *J* = 6.7 Hz), 1.68-1.82 (4H, m), 1.82-2.04 (3H, m), 2.19-2.28 (2H, m), 2.28-2.42 (3H, m), 2.51-2.70 (3H, m), 3.38 (1H, t, *J* = 8.9 Hz), 3.80-3.91 (1H, m), 4.01 (1H, t, *J* = 7.3 Hz), 5.01-5.10 (1H, m), 5.10-5.48 (3H, br s), 5.48-5.70 (2H, m), 6.74 (1H, t, *J* = 7.3 Hz), 6.87-6.97 (2H, m); IR(KBr)

3380, 2970, 2920, 2880, 1710, 1440, 1250 cm^{-1}; $[\alpha]_D$ = +117.37° (c 1.0, EtOH); LRMS m/z 398 (M^+); HRMS calcd for $C_{24}H_{30}O_5$ 398.2093, found 398.2073.

(8*S*,9*S*,16*R*)-Enone (**24b**)

To a solution of acetate (**23a**) (53.6 g, 0.154 mol) and *N,N'*-dicyclohexylcarbodiimide (38.0 g, 0.184 mol) in THF (270 mL) were added DMSO (164 mL, 2.31 mol), trifluoroacetic acid (2.3 mL, 0.031 mol), and pyridine (2.5 mL, 0.031 mol). After stirring at rt for 10 h to give an aldehyde, the reaction mixture was cooled in an ice bath.

To a suspension of 60% NaH (8.06 g, 0.202 mol) in THF (180 mL) was added a solution of Wadsworth reagent (**22**) (48.3 g, 0.208 mol) in THF (100 mL) below 25℃. The solution was cooled in an ice bath. To the solution of sodium salt of Wadsworth reagent was added the reaction mixture of the aldehyde below 10℃. The resulting suspension was stirred for 3 h and treated with AcOH (12.1 mL, 0.211 mol). To the mixture was added cyclohexane (300 mL) and the insoluble solid was filtered off. The filtrate was concentrated and the resulting residue was dissolved in EtOAc. The organic layer was washed with brine 3 times and each brine layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (EtOAc/cyclohexane = 1/5) to give (8*S*,9*S*,16*R*)-enone (**24b**) (69.0 g, 98.7%) as an oil; ^{1}H-NMR δ 1.21 (3H, d, *J* = 6.7 Hz), 1.70-1.82 (6H, m), 1.85-2.02 (2H, m), 2.08-2.53 (5H, m), 2.53-2.70 (3H, m), 2.83-3.04 (2H, m), 3.66(3H, s), 3.60-3.73 (1H, m), 5.00 (1H, q, *J* = 6.1 Hz), 5.18-5.28 (1H, m), 6.30 (1H, dd, *J* = 15.9, 1.2 Hz), 6.71-6.90 (2H, m), 6.90-6.97 (2H, m); IR (neat) 2950, 1732, 1450, 1365, 1230, 1030 cm^{-1}; $[\alpha]_D$ = +102.50° (c 1.0, EtOH); LRMS m/z 452 (M^+); HRMS calcd for $C_{27}H_{32}O_6$ 452.2199, found 452.2222.

(8*S*,9*S*,16*R*)-Methyl ester (**25b**)

To a solution of (8*S*,9*S*,16*R*)-enone (**24b**) (69 g, 0.152 mol) and $CeCl_3 \cdot 7H_2O$ (34.1 g, 91.5 mmol) in MeOH (1.25 L) was added $NaBH_4$ (2.90 g, 76.7 mmol). To the solution was added saturated $NaHCO_3$ aqueous solution (75 mL). The mixture was stirred for 1 h and filtered. The obtained filtrate was concentrated and the residue was treated with EtOAc and brine. The organic layer was separated and the aqueous layer was extracted with EtOAc 3 times. Each organic layer was washed with brine and combined. The organic layer was dried over

$MgSO_4$ and concentrated to give an oil (64.2 g).

The residue was dissolved in MeOH (1 L) and treated with 4.85 M NaOMe (6.0 mL, 29.1 mmol). The solution was stirred at rt for 20 h and neutralized by addition of AcOH (2 mL, 35 mmol). The solution was concentrated and the residue was treated with a mixture of EtOAc (900 mL) and H_2O (15 mL). The resulting solution was dried over $MgSO_4$ (40 g) and filtered. The filtrate was concentrated to give an oil (64.8 g). The residue was purified by column chromatography (EtOAc/cyclohexane = 2/3-2/1) to give (8*S*,9*S*,16*R*)-methyl ester (**25b**) (18.5 g, 29.5%), its epimer at C-15 (**26b**) (24.7 g, 39.4%), and a mixture of **25b** and **26b** (5.7 g, 9.1%).

(8*S*,9*S*,16*R*)-methyl ester (**25b**)

mp 101.0-102.5℃ (EtOAc/cyclohexane); ^{1}H-NMR δ 1.00 (3H, d, *J* = 6.7 Hz), 1.70-1.83 (4H, m), 1.83-2.15 (4H, m), 2.18-2.43 (4H, m), 2.52-2.90 (5H, m), 3.47 (1H, t, *J* = 8.2 Hz), 3.64 (3H, s), 3.80-3.92 (1H, m), 4.14 (1H, t, *J* = 5.8 Hz), 5.02-5.12 (1H, m), 5.52-5.70 (2H, m), 6.76 (1H, t, *J* = 7.3 Hz), 6.94 (2H, d, *J* = 7.3 Hz); IR (KBr) 3580, 3420, 2960, 2940, 2880, 1710, 1435, 1250 cm^{-1}; $[\alpha]_D$ = +124.54° (c 1.0, EtOH); LRMS m/z 412 (M^+); HRMS calcd for $C_{25}H_{32}O_5$ 412.2250, found 412.2226.

its epimer at C-15 (**26b**)

mp 79.0-81.0℃ (EtOAc/cyclohexane); ^{1}H-NMR δ 1.02 (3H, d, *J* = 6.7 Hz), 1.73-1.85 (4H, m), 1.85-2.05 (3H, m), 2.20-2.36 (6H, m), 2.49 (1H, q, *J* = 7.9 Hz), 2.55-2.68 (3H, m), 3.38 (1H, t, *J* = 8.4 Hz), 3.64 (3H, s), 3.89-4.00 (1H, m), 4.09 (1H, t, *J* = 5.8 Hz), 5.05-5.14 (1H, m), 5.60-5.78 (2H, m), 6.76 (1H, t, *J* = 7.3 Hz), 6.92-7.01 (2H, m); IR (KBr) 3550, 3420, 2960, 2930, 2880, 1720, 1450, 1240, 1020 cm^{-1}; $[\alpha]_D$ = +62.87° (c 1.0, EtOH); LRMS m/z 412 (M^+); HRMS calcd for $C_{25}H_{32}O_5$ 412.2250, found 412.2256.

The obtained epimer at C-15 (**26b**) (24.7 g, 0.0599 mol) was converted into (8*S*,9*S*,16*R*)-methyl ester (**25b**) by oxidation using MnO_2, followed by reduction using $CeCl_3 \cdot 7H_2O$ and $NaBH_4$ in MeOH in the same manner as with **26a**. The concentrate obtained from the work-up of the reaction was chromatographed together with a mixture of **25b** and **26b** above-mentioned. The recycle process was repeated 3 times to give (8*S*,9*S*,16*R*)-methyl ester (**25b**) (38.0 g, 60.7%) in total.

(8*S*,9*S*,16*R*)-Carboxylic acid (6)

To a solution of (8*S*,9*S*,16*R*)-methyl ester (**25b**) (28.7 g, 0.0696 mol) in MeOH (0.7 L) was added 2 N NaOH aqueous solution (125 mL, 0.25 mol) in an ice bath at such a rate that the temperature of reaction solution was below 10℃. The solution was stirred at rt for 32 h. The solution was concentrated below 40℃ and the resulting residue was dissolved in H_2O (150 mL). The solution was washed with a mixture of ether and cyclohexane (1/1, 300 mL) and cooled below 10℃. The solution was slowly neutralized with citric acid monohydrate (17.7 g, 84.2 mmol) and extracted with EtOAc 3 times. Each organic layer was washed with brine and combined. The organic layer was dried over $MgSO_4$ and concentrated to give 33 g. The residue was purified by column chromatography 2 times (1st: EtOAc/cyclohexane = 1/1 ～EtOAc containing 1% H_2O, 2nd: 2-propanol/*n*-hexane = 1/10). The obtained acid was dispersed in a mixture of EtOH (2 mL) and H_2O (40 mL) and freeze-dried to give (8*S*,9*S*,16*R*)-carboxylic acid (**6**) (13.66 g, 49.3%) as an oil; ^{1}H-NMR δ 1.02 (3H, d, *J* = 6.7 Hz), 1.70-1.85 (4H, m), 1.85-2.15 (4H, m), 2.18-2.45 (4H, m), 2.52-2.71 (3H, m), 3.40 (1H, t, *J* = 8.4 Hz), 3.82-3.95 (1H, m), 4.08-4.18 (1H, m), 4.60-5.30 (3H, br s), 5.02-5.12 (1H, m), 5.50-5.74 (2H, m), 6.75 (1H, t, *J* = 7.3 Hz), 6.94 (2H, d, *J* = 7.3 Hz); IR(KBr) 3400, 2970, 2930, 2880, 1710, 1450, 1250 cm^{-1}; $[\alpha]_D$=+115.49° (c 1.1, EtOH); LRMS m/z 398 (M^+); HRMS calcd for $C_{24}H_{30}O_5$ 398.2093, found 398.2090.

(8*R*,9*R*,16*R*)-Enone (**24c**)

To a solution of acetate (**23b**) (55 g, 0.158 mol) and *N,N'*-dicyclohexylcarbodiimide (39.0 g, 0.189 mol) in THF (280 mL) were added DMSO (168 mL, 2.37 mol), trifluoroacetic acid (2.3 mL, 0.0299 mol), and pyridine (2.5 mL, 0.0309 mol). After stirring at rt for 10 h to give an aldehyde, the reaction mixture was cooled in an ice bath.

To a suspension of 60% NaH (8.27 g, 0.207 mol) in THF (180 mL) was added a solution of Wadsworth reagent (**22**) (49.5 g, 0.213 mol) in THF (100 mL) below 25℃. The solution was cooled in an ice bath. To the solution of sodium salt of Wadsworth reagent was added the reaction mixture of the aldehyde below 10℃. The resulting suspension was stirred for 3 h and treated with AcOH (12.1 mL, 0.211 mol). To the mixture was added cyclohexane (300 mL) and the insoluble solid was filtered off. The filtrate was concentrated and the resulting residue was dissolved in EtOAc. The organic layer was washed with brine 3 times and each brine layer was extracted with EtOAc. The combined organic layers were dried over

$MgSO_4$ and concentrated. The residue was purified by column chromatography (EtOAc / cyclohexane = 1/5) to give (8*R*,9*R*,16*R*)-enone (**24c**) (64.0 g, 89.2%) as an oil; ^{1}H-NMR δ 1.21 (3H, d, *J* = 7.3 Hz), 1.70-1.82 (6H, m), 1.87-2.02 (2H, m), 2.08-2.52 (5H, m), 2.53-2.70 (3H, m), 2.87-3.00 (2H, m), 3.66 (3H, s), 3.60-3.73 (1H, m), 5.02 (1H, q, *J* = 6.1 Hz), 5.18-5.28 (1H, m), 6.29 (1H, d, *J* = 15.3 Hz), 6.78 (1H, t, *J* = 7.3 Hz), 6.83 (1H, dd, *J* = 15.3, 8.2 Hz), 6.95 (1H, d, *J* = 7.3 Hz), 6.97 (1H, d, *J* = 7.3 Hz); IR (neat) 2950, 1732, 1442, 1368, 1220, 1030 cm^{-1}; $[\alpha]_D$ = -113.74° (c 1.0, EtOH); LRMS m/z 452 (M^+); HRMS calcd for $C_{27}H_{32}O_6$ 452.2199, found 452.2199.

(8*R*,9*R*,16*R*)-Methyl ester (25c)

To a solution of (8*R*,9*R*,16*R*)-enone (**24c**) (64 g, 0.141 mol) and $CeCl_3 \cdot 7H_2O$ (31.6 g, 84.8 mmol) in MeOH (1.2 L) was added $NaBH_4$ (2.685 g, 71.0 mmol). To the solution was added saturated $NaHCO_3$ aqueous solution (70 mL). The mixture was stirred for 1 h and filtered. The obtained filtrate was concentrated and the residue was treated with EtOAc and brine. The organic layer was separated and the aqueous layer was extracted with EtOAc 3 times. Each organic layer was washed with brine and combined. The organic layer was dried over $MgSO_4$ and concentrated to give an oil (62.2 g).

The residue was dissolved in MeOH (1 L) and treated with 4.85 M NaOMe (5.5 mL, 26.7 mmol). The solution was stirred at rt for 20 h and neutralized by addition of AcOH (1.9 mL, 33 mmol). The solution was concentrated and the residue was treated with a mixture of EtOAc (800 mL) and H_2O (10 mL). The resulting mixture was dried over $MgSO_4$ (30 g) and filtered. The filtrate was concentrated to give an oil (62.4 g). The residue was purified by column chromatography (EtOAc/cyclohexane = 2/3-2/1) to give (8*R*,9*R*,16*R*)-methyl ester (**25c**) (19.9 g, 34.2%), its epimer at C-15 (**26c**) (26.2 g, 45.0%), and a mixture of **25c** and **26c** (6.1 g, 10.5%).

(8*R*,9*R*,16*R*)-methyl ester (**25c**)

mp 82.0-84.0℃ (EtOAc/cyclohexane); ^{1}H-NMR δ 0.98 (3H, d, *J* = 7.3 Hz), 1.68-1.82 (4H, m), 1.82-2.02 (3H, m), 2.20-2.28 (2H, m), 2.28-2.42 (3H, m), 2.53-2.72 (3H, m), 3.10 (2H, br s), 3.39 (1H, t, *J* = 9.2 Hz), 3.64 (3H, s), 3.80-3.91 (1H, m), 4.01 (1H, t, *J* = 7.3 Hz), 5.01-5.10 (1H, m), 5.47-5.72 (2H, m), 6.75 (1H, t, *J* = 7.3 Hz), 6.86-6.96 (2H, m); IR (KBr) 3580, 3400, 2970, 2925, 2880, 1710, 1435, 1240 cm^{-1}; $[\alpha]_D$ = -115.13° (c 1.0, EtOH); LRMS m/z 412 (M^+);

HRMS calcd for $C_{25}H_{32}O_5$ 412.2250, found 412.2258.

its epimer at C-15 (**26c**)

mp 121.0-122.5℃ (EtOAc/cyclohexane); ^{1}H-NMR δ 1.01 (3H, d, *J* = 7.3 Hz), 1.79 (3H, t, *J* = 2.4 Hz), 1.80-2.05 (4H, m), 2.05-2.27 (4H, m), 2.32 (2H, t, *J* = 7.3 Hz), 2.49 (1H, q, *J* = 7.9 Hz), 2.55-2.70 (3H, m), 3.47 (1H, t, *J* = 8.5 Hz), 3.65 (3H, s), 3.89-3.98 (1H, m), 4.23 (1H, t, *J* = 4.6 Hz), 5.05-5.14 (1H, m), 5.59-5.78 (2H, m), 6.76 (1H, t, *J* = 7.6 Hz), 6.90-6.99 (2H, m); IR (KBr) 3540, 3420, 2970, 2930, 2880, 1715, 1440, 1240, 1020 cm^{-1}; $[\alpha]_D$ = -65.24° (c 1.0, EtOH); LRMS m/z 412 (M^+); HRMS calcd for $C_{25}H_{32}O_5$ 412.2250, found 412.2247.

The obtained epimer at C-15 (**26c**) (24.7 g, 0.0599 mol) was converted into (8*R*,9*R*,16*R*)-methyl ester (**25c**) by oxidation using MnO_2, followed by reduction using $CeCl_3 \cdot 7H_2O$ and $NaBH_4$ in MeOH in the same manner as with **26a**. The concentrate obtained from the work-up of the reaction was chromatographed together with a mixture of **25c** and **26c** above-mentioned. The recycle process was repeated 3 times to give (8*R*,9*R*,16*R*)-methyl ester (**25c**) (38.2 g, 65.8%) in total.

(8*R*,9*R*,16*R*)-Carboxylic acid (7)

To a solution of (8*R*,9*R*,16*R*)-methyl ester (**25c**) (28.9 g, 0.0701 mol) in MeOH (0.8 L) was added 2 N NaOH aqueous solution (130 mL, 0.26 mol) in an ice bath at such a rate that the temperature of reaction solution was below 10℃. The solution was stirred at rt for 30 h. The solution was concentrated below 40℃ and the resulting residue was dissolved in H_2O (150 mL). The solution was washed with a mixture of ether and cyclohexane (1/1, 300 mL) and cooled below 10℃. The solution was slowly neutralized with citric acid monohydrate (18.5 g, 0.088 mol) and extracted with EtOAc 3 times. Each organic layer was washed with brine and combined. The organic layer was dried over $MgSO_4$ and concentrated to give 33 g. The residue was purified by column chromatography 2 times (1st: EtOAc/cyclohexane = 1/1 ～EtOAc containing 1% H_2O, 2nd: 2-propanol/*n*-hexane = 1/10). The obtained acid was dispersed in a mixture of EtOH (2 mL) and H_2O (35 mL) and freeze-dried to give (8*R*,9*R*,16*R*)-carboxylic acid (**7**) (17.22 g, 61.6%); mp 61.0-63.0℃; ^{1}H-NMR δ 0.97 (3H, d, *J* = 6.7 Hz), 1.68-1.82 (4H, m), 1.82-2.04 (3H, m), 2.19-2.28 (2H, m), 2.28-2.42 (3H, m), 2.51-2.70 (3H, m), 3.37 (1H, t, *J* = 9.2 Hz), 3.80-3.91 (1H, m), 4.02 (1H, t, *J* = 7.3 Hz), 5.01-5.10 (1H, m), 5.10-5.48 (3H, br s), 5.48-5.70 (2H, m), 6.74 (1H, t, *J* = 7.3 Hz), 6.92 (2H, t, *J* = 7.3 Hz); IR

(KBr) 3380, 2970, 2920, 2880, 1710, 1440, 1250 cm^{-1}; $[\alpha]_D$ = -115.16° (c 1.0, EtOH); LRMS m/z 398 (M^+); HRMS calcd for $C_{24}H_{30}O_5$ 398.2093, found 398.2089.

(8*R*,9*R*,16*S*)-Enone (**24d**)

To a solution of acetate (**23b**) (55 g, 0.158 mol) and *N,N'*-dicyclohexylcarbodiimide (39.0 g, 0.189 mol) in THF (280 mL) were added DMSO (168 mL, 2.37 mol), trifluoroacetic acid (2.3 mL, 0.030 mol), and pyridine (2.5 mL, 0.031 mol). After stirring at rt for 10 h to give an aldehyde, the reaction mixture was cooled in an ice bath.

To a suspension of 60% NaH (8.27 g, 0.207 mol) in THF (180 mL) was added a solution of Wadsworth reagent (**19**) (49.5 g, 0.213 mol) in THF (100 mL) below 25℃. The solution was cooled in an ice bath. To the solution of sodium of Wadsworth reagent was added the reaction mixture of the aldehyde below 10℃. The resulting suspension was stirred for 3 h and treated with AcOH (12.1 mL, 0.211 mol). To the mixture was added cyclohexane (300 mL) and the insoluble solid was filtered off. The filtrate was concentrated and the resulting residue was dissolved in EtOAc. The organic layer was washed with brine 3 times and each brine layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (EtOAc/cyclohexane = 1/5) to give (8*R*,9*R*,16*S*)-enone (**24d**) (65.0 g, 91.1%) as an oil; ^{1}H-NMR δ 1.21 (3H, d, *J* = 6.7 Hz), 1.70-1.81 (6H, m), 1.85-2.02 (2H, m), 2.08-2.53 (5H, m), 2.53-2.70 (3H, m), 2.83-3.01 (2H, m), 3.66 (3H, s), 3.60-3.73 (1H, m), 5.00 (1H, q, *J* = 6.1 Hz), 5.18-5.28 (1H, m), 6.29 (1H, d, *J* = 15.3 Hz), 6.78 (1H, t, *J* = 7.3 Hz), 6.83 (1H, dd, *J* = 15.3, 8.2 Hz), 6.90-6.97 (2H, m); IR (neat) 2950, 1735, 1450, 1365, 1230, 1030 cm^{-1}; $[\alpha]_D$ = -103.55° (c 1.4, EtOH); LRMS m/z 452 (M^+); HRMS calcd for $C_{27}H_{32}O_6$ 452.2196, found 452.2176.

(8*R*,9*R*,16*S*)-Methyl ester (**25d**)

To a solution of (8*R*,9*R*,16*S*)-enone (**24d**) (65 g, 0.144 mol) and $CeCl_3 \cdot 7H_2O$ (32.0 g, 85.9 mmol) in MeOH (1.2 L) was added $NaBH_4$ (2.725 g, 72.0 mmol). To the solution was added saturated $NaHCO_3$ aqueous solution (70 mL). The mixture was stirred for 1 h and filtered. The obtained filtrate was concentrated and the residue was treated with EtOAc and brine. The organic layer was separated and the aqueous layer was extracted with EtOAc 3 times. Each organic layer was washed with brine and combined. The organic layer was dried over

$MgSO_4$ and concentrated to give an oil (61.2 g).

The residue was dissolved in MeOH (1 L) and treated with 4.85 M NaOMe (5.5 mL, 26.7 mmol). The solution was stirred at rt for 20 h and neutralized by addition of AcOH (1.9 mL, 33 mmol). The solution was concentrated and the residue was treated with a mixture of EtOAc (1 L) and H_2O (15 mL). The resulting mixture was dried over $MgSO_4$ (40 g) and filtered. The filtrate was concentrated to give an oil (62 g). The residue was purified by column chromatography (EtOAc/cyclohexane = 2/3-2/1) to give (8*R*,9*R*,16*S*)-methyl ester (**25d**) (16.4 g, 27.6%), its epimer at C-15 (**26d**) (25.3 g, 42.6%), and a mixture of **25d** and **26d** (4.8 g, 8.1%).

(8*R*,9*R*,16*S*)-methyl ester (**25d**)

mp 102.0-104.0℃ (EtOAc/cyclohexane); ^{1}H-NMR δ 1.02 (3H, d, *J* = 6.7 Hz), 1.70-1.83 (4H, m), 1.83-2.15 (4H, m), 2.18-2.43 (4H, m), 2.52-2.90 (5H, m), 3.41 (1H, t, *J* = 8.9 Hz), 3.65 (3H, s), 3.80-3.92 (1H, m), 4.14 (1H, t, *J* = 5.8 Hz), 5.02-5.12 (1H, m), 5.52-5.71 (2H, m), 6.76 (1H, t, *J* = 7.3 Hz), 6.94 (2H, d, *J* = 7.3 Hz); IR (KBr) 3580, 3420, 2960, 2940, 2880, 1710, 1435, 1250 cm^{-1}; $[\alpha]_D$ = -124.02° (c 1.0, EtOH); LRMS m/z 412 (M^+); HRMS calcd for $C_{25}H_{32}O_5$ 412.2250, found 412.2246.

its epimer at C-15 (**26d**)

mp 80.0-82.0 (EtOAc/cyclohexane); ^{1}H-NMR δ 1.00 (3H, d, *J* = 7.3 Hz), 1.73-1.85 (4H, m), 1.85-2.05 (3H, m), 2.05-2.28 (4H, m), 2.32 (2H, t, *J* = 7.3 Hz), 2.50 (1H, q, *J* = 7.3 Hz), 2.55-2.68 (3H, m), 3.49 (1H, t, *J* = 8.5 Hz), 3.65 (3H, s), 3.89-4.00 (1H, m), 4.09 (1H, t, *J* = 6.1 Hz), 5.07-5.16 (1H, m), 5.60-5.79 (2H, m), 6.77 (1H, t, *J* = 7.6 Hz), 6.92-7.01 (2H, m); IR (KBr) 3550, 3350, 2950, 2930, 2900, 1725, 1440, 1210, 1185, 1000 cm^{-1}; $[\alpha]_D$ = -59.70° (c 1.0, EtOH); LRMS m/z 412 (M^+); HRMS calcd for $C_{25}H_{32}O_5$ 412.2250, found 412.2224.

The obtained epimer at C-15 (**26d**) (24.3 g, 0.0589 mol) was converted into (8*R*,9*R*,16*S*)-methyl ester (**25d**) by oxidation using MnO_2, followed by reduction using $CeCl_3 \cdot 7H_2O$ and $NaBH_4$ in MeOH in the same manner as with **26a**. The concentrate obtained from the work-up of the reaction was chromatographed together with a mixture of **25d** and **26d** above-mentioned. The recycle process was repeated 3 times to give (8*R*,9*R*,16*S*)-methyl ester (**25d**) (37.4 g, 63.0%) in total.

(8*R*,9*R*,16*S*)-Carboxylic acid (8)

To a solution of (8*R*,9*R*,16*S*)-methyl ester (**25d**) (30.0 g, 0.0727 mol) in MeOH (0.8 L) was added 2 N NaOH aqueous solution (110 mL, 0.22 mol) in an ice bath at such a rate that the temperature of reaction solution was below 10℃. The solution was stirred at rt for 38 h. The solution was concentrated below 40℃ and the resulting residue was dissolved in H_2O (150 mL). The solution was washed with a mixture of ether and cyclohexane (1/1, 300 mL) and cooled below 10℃. The solution was slowly neutralized with citric acid monohydrate (18.5 g, 0.088 mol) and extracted with EtOAc 3 times. Each organic layer was washed with brine and combined. The organic layer was dried over $MgSO_4$ and concentrated to give 33 g. The residue was purified by column chromatography 2 times (1st: EtOAc/cyclohexane = 1/1 ～EtOAc containing 1% H_2O, 2nd: 2-propanol/*n*-hexane = 1/10). The obtained acid was dispersed in a mixture of EtOH (2 mL) and H_2O (40 mL) and freeze-dried to give (8*R*,9*R*,16*S*)-carboxylic acid (**8**) (18.61 g, 64.2%) as an oil; ^{1}H-NMR δ 1.02 (3H, d, *J* = 6.7 Hz), 1.70-1.85 (4H, m), 1.85-2.15 (4H, m), 2.18-2.45 (4H, m), 2.52-2.71 (3H, m), 3.39 (1H, t, *J* = 8.9 Hz), 3.82-3.93 (1H, m), 4.07-4.16 (1H, m), 4.80-5.50 (3H, br s), 5.01-5.10 (1H, m), 5.50-5.70 (2H, m), 6.75 (1H, t, *J* = 7.9 Hz), 6.94 (2H, d, *J* = 7.9 Hz); IR (KBr) 3400, 2920, 1710, 1445, 1250, 1190 cm^{-1}; $[\alpha]_D$ = -118.05° (c 1.0, EtOH); LRMS m/z 398 (M^+); HRMS calcd for $C_{24}H_{30}O_5$ 398.2093, found 398.2083.

REFERENCES

1. (a) S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature*, 1976, **263**, 663. (b) W. Bartmann and G. Beck, G. *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 751. (c) R. C. Nickolson, M. H. Town, and H. Vorbruggen, *Med. Res. Rev*., 1985, **5**, 1. (d) P. W. Collins, S. W. Djuric, *Chem. Rev*., 1993, **93**, 1533.
2. K. Ohno, H. Nagase, K. Matsumoto, H. Nishiyama, and S. Nishio, ´In Advances in Prostaglandin, Thromboxane, and Leukotriene Research,´ Vol. 15, ed. by O. Hayashi and S. Yamamoto, Ravan Press, New York, 1985, pp. 279-281.
3. K. Ohno, H. Nishiyama, H. Nagase, K. Matsumoto, and M. Ishikawa, *Tetrahedron Lett.,* 1990, **31**, 4489.
4. H. Nagase, K. Matsumoto, H. Yoshiwara, A. Tajima, and K. Ohno, *Ibid*., 1990, **31**, 4493.
5. H. Nagase, K. Matsumoto, and H. Nishiyama, *Yuki Gosei Kagaku Kyokaishi (J. Synth.*

Org. Chem. Jpn.), 1996, **54**, 1055.

6. H. Wakita, K. Matsumoto, H. Yoshiwara, Y. Hosono, R. Hayashi, H. Nishiyama, and H. Nagase, *Tetrahedron*,1999, **55**, 2449.
7. H. Wakita, H. Yoshiwara, A. Tajima, Y. Kitano, and H. Nagase, *Tetrahedron: Asymmetry,* 1999, **10**, 4099.
8. M. M. Hann, P. G. Sammes, P. D. Kennewell, and J. B. Taylor, *J. Chem. Soc., Perkin Trans. 1,* 1982, 307.
9. (a) W. Skuballa, E. Schillinger, C. Sturzebecher, and H. Vorbruggen, *J. Med. Chem.,* 1986, **29**, 313. (b) M. Harre, J. Trabandt, and J. Westermann, *Liebigs Ann. Chem.,* 1989, 1081. (c) E. J. Corey and C. J. Helal, *Tetrahedron Lett.,* 1997, **38**, 7511. (d) We obtained the starting materials, (-)- and (+)-2-methylhexynic acids by optical resolution. The result of the study will be described in detail in due course.
10. J-L. Luche, *J. Am. Chem. Soc.*, 1978, **100**, 2226.